MANAGEMENT OF HYPERTENSIVE DISORDERS IN PREGNANCY

Dr. Swati Rathore, MD, Dr. Anuja Abraham, MD, Dr. Santosh Benjamin, MD. Department of Obstetrics and Gynaecology, Christian Medical College, Vellore.

Introduction

Hypertension is a multi-system disorder with varied and still unknown etiology with an unpredictable outcome. Early diagnosis and careful monitoring of patients with preeclampsia is the cornerstone in management of pre-eclampsia. Careful timing of delivery will decrease the maternal and perinatal morbidity.

Hypertensive disorders occur in 5-10% of all pregnancies and account for 16% of maternal deaths. The incidence of pre-eclampsia is 3-5% of pregnancies. Eclampsia occurs in 1 in 2000 pregnancies in developed countries with the incidence being much higher in developing countries.

Classification of hypertensive disorders in pregnancy

The Working group classification describes 4 types of hypertensive disorders in pregnancy.

1. **Gestational hypertension**: When the systolic BP is >140 OR diastolic BP > 90mm Hg for the first time during pregnancy, after 20 weeks gestation and not associated with proteinuria and BP returns to normal before 12 weeks postpartum, it defined as gestational hypertension. Pregnancy outcome in gestational hypertension is favorable.

2. **Pre-eclampsia**: Gestational hypertension associated with proteinuria with onset after 20 weeks of gestation. It can be divided into mild and severe forms.

   - **Mild pre-eclampsia**
     - BP ≥ 140/90mmhg after 20 weeks gestation
     - Proteinuria ≥ 300mg/24hrs or ≥ 1+ on dipstick

   - **Severe pre-eclampsia** is characterized by one or more of the following:
     - BP ≥160/110mmhg
     - Proteinuria ≥ 2g/24 hrs or ≥ 2+ on dipstick
     - Serum Creatinine > 1.2mg/dl
     - Platelet < 1 lakh/cc
     - Increased LDH
     - Increased AST/ALT
     - Persistent headache/visual scotomata
     - Persistent epigastric pain

3. **Chronic hypertension**: When the systolic or diastolic BP is ≥140/90 mmHg prior to conception or before 20 weeks of gestation or if it persists after 12 weeks postpartum. Prevalence of chronic hypertension in women of childbearing age increases with age.

4. **Superimposed pre-eclampsia on chronic hypertension**: New onset proteinuria ≥ 300mg/24hrs in a hypertensive patient who had no proteinuria before 20 weeks of gestation OR sudden increase in proteinuria or BP or Platelet <1 lakh/cc
in women with hypertension and proteinuria before 20 weeks of GA.

**Why do we need to treat hypertension in pregnancy?**

**Rationale for treatment**

1. To decrease the incidence of indicated pre-term delivery due to development of pre-eclampsia
2. To decrease the incidence of placental abruption
3. To improve foetal growth

The level of blood pressure is the most important factor, as treatment of severe hypertension (systolic BP ≥160 mmHg and/or diastolic BP ≥110 mmHg) prevents maternal complications like intracranial haemorrhage and reduces the likelihood of end organ damage. The role of anti-hypertensives in mild-moderate hypertension is not very clear.

The underlying etiology of the elevated blood pressure should be taken into account. Women with chronic hypertension may tolerate higher blood pressures better than previously normotensive women with acute hypertension due to preeclampsia. Timing of delivery is also a factor; if prompt cesarean delivery is planned, antihypertensive therapy may not be needed as anesthesia can lower the blood pressure.

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**Risks of treatment**

Overzealous reduction of blood pressure must be avoided because of associated risks.

In severe pre-eclampsia, lowering the blood pressure can mask an accessible marker for treatment (induction of labour and delivery). The rising blood pressure in pre-eclampsia is masked leading to a false sense of reassurance.

Anti-hypertensives can affect the foetus in two ways - directly by influencing the umbilical or foetal cardiovascular circulation and indirectly by lowering uteroplacental blood flow.

**Indications for use of anti-hypertensives**

1. Chronic hypertension with severe disease is a definite indication. The role of antihypertensives is unclear in mild to moderate hypertension.
2. Conservative management of severe pre eclampsia or gestational hypertension at < 34 weeks of gestation.
3. Severe hypertension in labour and post partum.

There is a lot of ambiguity among international bodies regarding the blood pressure cutoff at which antihypertensives need to be started. The general consensus is that a systolic blood pressure above 160 mmHg and a diastolic above 100 mm Hg require treatment.

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**GENERAL MANAGEMENT OF HYPERTENSION IN PREGNANCY**

**Pre-eclampsia:**

Management of PE continues to pose a challenge. This is an unpredictable disorder where the definitive cure is termination of pregnancy. Therefore management is directed towards early detection and amelioration of its progression.

The goal is prolongation of pregnancy to achieve fetal maturity, thereby improve perinatal outcome.

**Monitoring**

**Antepartum surveillance:** is directed towards monitoring of mother and baby. The patient is hospitalized and the following are carried out:

- BP is checked every 4 to 6 hours
- Urine protein levels are checked twice a day
- Blood investigations to assess serum creatinine, liver enzymes, platelets and lactate dehydrogenase (LDH)
• Signs and symptoms of impending eclampsia are looked for
• Fetal wellbeing is assessed

**Fetal monitoring in pre-eclampsia and gestational hypertension:**

• Daily fetal movement count, Non stress test (NST)
• Ultrasound (fetal weight estimation, amniotic fluid levels, and flow in the umbilical artery).

Fetal growth restriction is a common complication of pre-eclampsia, hence the growth should be monitored clinically and with ultrasound. Each case must be evaluated individually and the benefits of delivery weighed against the potential risk of continuing pregnancy.

**Timing of delivery in pregnancy complicated by hypertension:**

Management is determined by the severity of the disease and the gestational age.

**Pregnancy > 37 weeks of gestation**, with persistent high BP will need induction of labor, and close maternal and fetal monitoring.

If pregnancy is < 34 weeks, labor should be induced after corticosteroids are administered to accelerate fetal lung maturity.

In cases of impending eclampsia, antihypertensives and prophylactic anticonvulsant therapy is urgently required. Blood pressure, proteinuria and fluid balance should be monitored carefully. Once the maternal condition is stabilized, pregnancy should be terminated, by induction of labor or caesarean section.

**Post natal monitoring**

In most of the cases of PE, the blood pressure, proteinuria and edema settle rapidly. The blood pressure should be monitored daily in the first few days and antihypertensives are indicated only when the diastolic pressure is persistently above 100 mm Hg or the systolic above 160 mm Hg. If antihypertensives are started, the dose can be adjusted according to the blood pressure readings. The blood pressure must be measured at 12 weeks postpartum and if still elevated, she is diagnosed to have chronic hypertension.

**Table 1: Commonly used antihypertensives**

<table>
<thead>
<tr>
<th>Antihypertensive</th>
<th>Dosage</th>
<th>Maximum dose/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyl dopa</td>
<td>250-500mg bd/tid/qid</td>
<td>2gm</td>
</tr>
<tr>
<td>Labetalol</td>
<td>100mg bd</td>
<td>800mg</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>10-20mg bd</td>
<td>80-120 mg</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>10-25mg bd</td>
<td>40-200mg</td>
</tr>
</tbody>
</table>

All antihypertensive drugs cross the placenta and no data from trials is available regarding which drug to choose over the others. The drugs available for treatment in pregnancy are centrally acting sympatholytics, calcium channel blockers, vasodilators, beta blockers and diuretics. The drugs absolutely contraindicated during pregnancy are ACE inhibitors and Angiotensin Receptor Blockers.

**Methyl dopa (centrally acting sympatholytic)**

• Methyl dopa has been widely used in pregnant women and its long-term safety for the fetus has been demonstrated. It is the most widely used antihypertensive drug.
Mechanism of action - Induces synthesis of alpha methylnorepinephrine in the central nervous system which stimulates alpha receptors leading to decreased sympathetic out flow from CNS.

It has a slow onset of action (3-6 hours) and takes 48 hours however for total anti-hypertensive effect. If blood pressure is therefore not under control in the first 48 hours, concurrent use of another drug like Nifedipine may be required.

**Adverse effects of methyl dopa**

**Common**
- Sedation
- Dry mouth
- Nasal stuffiness
- Headache
- Depression

**Uncommon**
- Vertigo
- Extrapyramidal signs
- Hemolytic anemia
- Leukopenia
- Thrombocytopenia
- Drug fever
- Hepatitis

**Labetolol**

It has both alpha- and beta-adrenergic blocking activity and is currently the drug of first choice as recommended by the NICE guidelines for acute control of blood pressure. It has a more rapid onset of action (in 2 hours) compared to methyldopa. It can be administered in the intravenous form for acute control or the oral form for maintenance therapy of blood pressure.

Mechanism of action: Blood pressure is lowered by reduction of vascular resistance without significant alteration of heart rate.

Half life – 6 hours

Dosage: Per day – It is started as 100 mg twice or thrice daily to a maximum of 800mg per day.

**Adverse effects**
- Bronchospasm
- Headache

**Calcium channel blockers**

**Mechanism of action:**
- Relaxes arterial smooth muscle
- Can be used in all trimesters.

Of the calcium channel blockers, nifedipine is widely used and has not been associated with any major problems. Short, intermediate and sustained release preparations are available. Although amlopidine is widely used in non-pregnant individuals, data recommending its use in pregnancy is limited. However, it shows promise because of its long duration of action.

Nifedipine can also be used for control of acute severe hypertension and studies have shown oral nifedipine and parenteral labetolol to be equally effective. (See next page)

Dose of Nifedipine - 10-20mg bd, max upto 80-120 mg/day

**Adverse effects of calcium channel blockers**
- Headache
- Flushing
- Peripheral oedema
- Maternal tachycardia
- Potential synergism when used with magnesium sulphate causing hypotension and neuromuscular blockade

**Vasodilators**
- Hydralazine is most commonly used in developed countries
- Half-life of 2-4 hours, effect with iv bolus in 5-20 min, effect lasting 2-6 hrs
- 40 – 200 mgs/day in 2-3 divided doses orally
For rapid action – IV boluses of 5 mg

**Adverse effects**
- Severe headache
- Reflex tachycardia
- Lupus like syndrome

**Diuretics**
Diuretics are only used to treat pulmonary edema that may occur and not for blood pressure control at all.

**Acute control of blood pressure in severe pre-eclampsia**
Drugs used for acute control of blood pressure:
- Labetalol
- Nifedipine
- Hydralazine
- Sodium Nitroprusside
- Nitroglycerine
- Prazocin

The choice of antihypertensive in a hypertensive crisis is left to the discretion of the obstetrician according to a Cochrane database review. The two most commonly used drugs are intravenous labetalol and oral nifedipine. The efficacy of these drugs has been compared and they have been found to be similar in efficacy.
- Nifedipine is given as 10 mg capsules at intervals of 15-20 minutes with a maximum dose of 120mg.
- The target blood pressure is around 140-150/80-90 and not lower than that.
- Intravenous labetalol can be used as a second line drug if the nifedipine has not controlled the blood pressure adequately. It is given either as an infusion or as IV boluses. The boluses start as 10mg and are incrementally increased to 20, 40 and 80 mg at intervals of 15-20 minutes if the blood pressure is still elevated. While using IV labetalol, the patient must be kept on a cardiac monitor due to the risk of bradycardia and cardiac rhythm abnormalities.
- If the above mentioned drugs still fail to control the blood pressure, nitroglycerine infusion can be used in an intensive care setting.
- Drugs like nimodipine, ketanserin and diazoxide however are best avoided.

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**Seizure prophylaxis in pre-eclampsia with magnesium**
Magnesium Sulphate (MgSO4) is the drug of choice for seizure prophylaxis in pre-eclampsia.

**Indications**
- Proteinuria of 2+ or greater as measured by dipstick in a catheterized urine specimen
- Serum creatinine more than 1.2 mg/dl
- Platelets less than 100,000/cc
- AST elevated two times above upper limit of normal range
- Persistent headache or scotomata

**Dosage**
Patients on MgSO4 need monitoring to avoid problems due to toxicity and adverse effects. The clinical effects with different serum concentrations is...
given in the table below.

<table>
<thead>
<tr>
<th>Magnesium level in meq/l</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-8</td>
<td>Therapeutic level</td>
</tr>
<tr>
<td>8-10</td>
<td>Loss of deep tendon reflexes</td>
</tr>
<tr>
<td>&gt;10</td>
<td>Respiratory depression</td>
</tr>
<tr>
<td>&gt;12</td>
<td>Respiratory arrest</td>
</tr>
</tbody>
</table>

**Magnesium sulphate**

Drug of choice for eclampsia and prevention of recurrence

**Mechanism of action:**
Probable NMDA antagonist, causes cerebral vasodilation and reduces cerebral ischemia, also smooth muscle relaxant

**Adverse effects**
Respiratory depression, respiratory and cardiac arrest

**Monitoring**
Deep tendon reflexes, 
Urine output, 
Respiratory rate

**Antidote in toxicity**
Calcium gluconate

**Monitoring a patient on MgSO4**

- Clinical parameters
  1. Presence of patellar reflex
  2. Urine output (at least 100ml in last 4 hours)
  3. Respiratory rate (>12/min)

- If any of these 3 parameters is absent, the MgSO4 dose is withheld/delayed

- 10ml of 10% Calcium gluconate used as antidote for toxicity.

**Prevention and treatment of eclampsia**

For women with eclampsia, the Collaborative Eclampsia Trial, established the superiority of magnesium sulphate over diazepam and phenytoin for the control of seizures with lesser incidence of pneumonia and need for ventilation for both the mother and baby. The Magpie Trial showed a reduction in the incidence of eclampsia also for women with preeclampsia treated with magnesium sulphate.

Magnesium sulphate is the drug of choice for treatment of women with eclampsia and for prevention of recurrence of further seizures. The mechanism of action is unclear. It probably acts as an N-methyl-D-aspartate (NMDA) antagonist. It causes cerebral vasodilatation and reduces cerebral ischemia. It is also a calcium antagonist, and a smooth muscle relaxant. It may lower intracellular calcium thus limiting transport of ions and proteins, which promote cerebral edema and seizure.

The side effects of magnesium sulphate are mainly due to its smooth muscle relaxant property. The most serious are respiratory depression, respiratory and cardiac arrest. Side effects are dose dependant with loss of deep tendon reflexes in the initial stages. Other clinical parameters to be monitored are urine output and respiratory rate. Hence clinical monitoring can be used for features of toxicity and serial magnesium levels need not be measured. In the event of toxicity, calcium gluconate is to be administered as antidote.

**Regimes for magnesium sulphate**

Table 3 describes the standard intramuscular and intravenous regimes used for the administration of magnesium sulphate for the management of severe pre-eclampsia and eclampsia.

Other regimes like the Dhaka regime (4gm IV loading dose, 6gm IM loading followed by 2.5 gm IM every 4th hourly) and Bhalla regime have been
The doses of magnesium sulphate used in these regimes are lower, the main concern being toxicity of higher doses. Alternative regimes have variations in the loading dose, variations in the dose and frequency of maintenance doses and in the duration of therapy.

Various studies on duration of postpartum magnesium sulphate have been described. Clinical parameters like blood pressure, urine output, urine protein based on dipstick and presence or absence of symptoms can be used to shorten the duration of prophylactic postpartum magnesium sulphate.

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**DRUG WARNING : Sofosbuvir + amiodarone = severe bradycardia**

The US Food and Drug Administration (FDA) is warning that serious bradycardia can occur when the antiarrhythmic drug amiodarone is taken together either with the hepatitis C combination drug ledipasvir/sofosbuvir or with sofosbuvir taken in combination with another direct acting antiviral (DDA) for the treatment of hepatitis C infection. Healthcare professionals are recommended not to prescribe sofosbuvir combined with another DDA with amiodarone. If combination is essential, cardiac monitoring for first 48 hours as an in-patient is recommended. FDA’s review of submitted postmarketing adverse event reports found that patients can develop a serious and life-threatening symptomatic bradycardia when taking the combination. The reports included the death of one patient due to cardiac arrest and 3 patients requiring placement of a pacemaker to regulate heart rhythms. The other patients recovered after discontinuing either the hepatitis C drugs or amiodarone or both. 6 of the cases occurred within 24 hours and the remaining 3 after 2 to 12 days. The cause of these events could not be determined.

Source: Pharmacy Bulletin published by Pharmacy service, CMC Vellore